REMARKS

This submission is in response to the non-final Office Action electronically mailed on June 23, 2008. Claims 1 and 21 have been amended to specify "an analgesically effective amount of morphine base monohydrate" and a controlled release chitosan polymer "in an amount effective to provide substantially linear absorption rates upon administration." Support for this amendment can be found, for example, in the claims as originally filed and on page 4, lines 1-5 of the application as-filed.

I. Statement Regarding March 12, 2008 Interview and Present Office Action

Applicant again notes the Interview between Applicant's representatives David Bernstein and the undersigned, Examiner Mercier and Supervisory Examiner Kishore. During the Interview, Supervisory Examiner Kishore agreed that U.S. Patent No. 5,629,011 (referred to herein as "Illum II") would be removed as a reference, although the Examiner reserved the right to find other references that teach the base monohydrate form of morphine. Contrary to the statements made in the interview, however, Illum II remains a reference in the present Office Action. Also contrary to the spirit of the interview, the Examiner has not relied upon a new reference to reject the presently pending claims. (Although the rejection now formally refers to the Merck Index, this reference was relied upon in the Office Action dated November 15, 2007). Further, the Applicant has never received a summary of the March 12, 2008 interview, and has been told that, contrary to MPEP 713.04, such summary was never prepared.

In view of the progress made during the March 12, 2008 interview, which progress has been ignored in the present Office Action, Applicants respectfully request that a better effort be made to advance prosecution. Applicants take issue with the Examiner's practice of copying and pasting prior rejections, while not substantively responding to Applicant's prior statements. Refusal to substantively consider Applicants prior remarks is most egregious on page 15 of the Office Action with the Examiner's "Response to Arguments." There, it was summarily noted that the Examiner was unable to locate an Exhibit which apparently made it impossible to further comment upon Applicant's comments. As would be clear from a reading of Applicant's response, this Exhibit was the Merck Index – a reference that the Examiner

referenced in the November 15, 2007 Office Action, and presumably in the possession of the Examiner. Applicants respectfully request that the Examiner make a better effort to advance prosecution by implementing the suggestions made by Examiner Kishore and removing (at least) Illum II as a reference. Applicants also request that the Examiner substantively respond to the Applicant's remarks made in this response.

In the interview, it was also noted that proposed claims directed to methods of treating pain comprising administering a controlled release morphine medicament, of the composition currently recited in presently pending claims 1 and 21, were allowable. These claims were submitted in a divisional application assigned Serial No. 12/049,893.

II. The Present Invention

Applicants have found that when combining the base monohydrate form of morphine with chitosan at specified molecular ratios, the resulting formulation provides substantially linear absorption upon administration. Such linear absorption provides a controlled increase in therapeutic plasma levels of morphine during the absorption or uptake phase after nasal administration. Such controlled absorption of morphine reduces the risk of overly rapid absorption and thus reduces the risk of overdose (see specification page 7, lines 8-18).

III. Objections to the Specification

The Examiner had objected to amendments to the specification made in Applicants' August 27, 2007 Response, previously arguing that:

> Applicant has submitted amendments to the specification, which are new matter. Applicant has presented amendments, which would change the release profile from first order to zero order kinetics

(November 15, 2007 Office Action, page 2, paragraph 2).

In the March 19, 2008 response, Applicants respectfully disagreed that new matter had been added, or that applicants have "changed" the release profile in any way.

Applicants noted that, the release profile is as originally set forth in the figures and examples of the application as-filed: a substantially linear absorption rate.

In response to these arguments, the Examiner alleges:

> Applicant has not demonstrated zero order kinetics in the figures of the application. Zero order kinetics is defined as reactions independent of concentration of the reactants. A reaction of zero order is demonstrated if concentration data are plotted versus time and the result is a straight line. The only figure with a straight line present is figure 6, however, the axis are AUC and dosage amounts. Furthermore, the plots are not drawn to scale and if drawn to scale, would not result in a linear plot.

(June 23, 2008 Office Action, pages 2-3).

Applicant respectfully disagrees. Initially, Applicant notes that the amendments to the specification refer to zero-order kinetics *during the absorption phase or uptake* of the morphine. *See, e.g,* paragraph beginning on page 7, line 8 of the application as-filed. Thus zero-order kinetics during the absorption or uptake phase is shown by a linear line (or a substantially linear line, mindful of, for example, measurement variances) when concentration data are plotted versus time.

The application as filed does indeed show zero-order kinetics during the absorption or uptake phase. For example, Figure 1 reproduced below demonstrates zero-order kinetics during the uptake of the morphine when administered with 15 mg of chitosan:

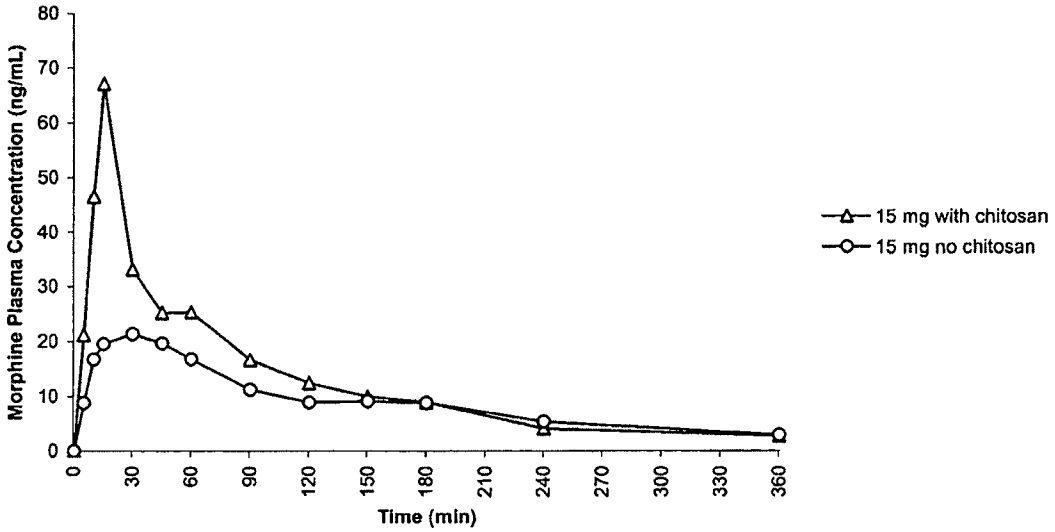

Figure 1 demonstrates that the uptake of morphine is linear in the chitosan-containing formulation, as compared to the non-linear uptake of the morphine when administered without chitosan. Linear uptake of the morphine is also shown in nasal, chitosan-containing formulations in Figures 2-5.

It is noted that Figure 1 *is* drawn to scale. By way of definition, it is well-established that so long as a given length on a respective axis denotes equal time or concentrations intervals, the figure is drawn to scale. In addition to Figure 1, shown above, Figures 2 – 5 are also drawn to scale. The Examiner's assertion that "the plots are not drawn to scale" is not understood by Applicants. Should the Examiner maintain this position, it is requested that this aspect of the Examiner's position be further clarified.

As the application does indeed demonstrate linear uptake of morphine, as shown for example in Figure 1 above, there is support to amend the specification to refer to zero-order kinetics during the absorption or uptake phase. Applicants request that this objection be withdrawn.

IV. Objection to Claim 6

Claim 6 is objected to for failing to further limit a claim from which it depends (claim 1). In response to Applicants argument that claim 1 does not require the use of *purified* morphine base monohydrate, the Examiner states:

> Applicant argues claim 6 further limits claim 1, since claim 1 does not require the use of purified morphine base monohydrate. Applicant also states in response to the 112, 2nd paragraph rejection of claim 6, that pharmaceutical grade morphine base monohydrate is generally purified. Therefore, it is submitted that the morphine in claim 1 is inherently purified and since Applicant has not provided a desired purity level, any morphine suitable for use in a pharmaceutical formulation would read on the instantly claimed morphine.

(June 23, 2008 Office Action, pages 3-4).

Applicants respectfully disagree with the Examiner's reasoning, which is inherently based on the premise that claim 1 requires that the composition be a pharmaceutical formulation for human administration. This is not necessarily the case, as claim 1 is broad enough to encompass, for example, compositions for research or animal-testing purposes. In such instances, the morphine base monohydrate need not necessarily be a pharmaceutical composition approved for human consumption, and thus need not necessarily contain purified morphine base monohydrate. Because claim 6 calls for purified morphine base monohydrate, applicants submit that claim 6 does indeed further limit claim 1. Applicants request that the objection to claim 6 be withdrawn.

V. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-2, 4-17, 20-23 stand rejected as indefinite. The Examiner asserts that the terms "therapeutically effective" and "an effective amount" are unclear, and that it is unclear exactly how much is effective and what the desired effect actually is.

In response to Applicants' arguments that these terms are definite to a person of ordinary skill in the art, the Examiner asserts:

> Applicant argues one of ordinary skill would be able to ascertain the effective amounts, however, the claims do not [recite] what the amount [is] effective for, i.e. pain management, or controlled increase in plasma levels during the absorption phase therefore, the claim language is deemed indefinite. It is not clear based on the claim language what the component is effective for.

(June 23, 2008 Office Action, pages 4-5)

While applicants respectfully disagree with the Examiner's rejection, the claims have been amended solely in order to advance prosecution. More particularly claims 1 and 21 have been amended to recite an analgesically effective amount of morphine base monohydrate, and a controlled release chitosan polymer in an amount effective to provide substantially linear absorption rates upon administration. Accordingly, the claim language now clearly describes what the morphine base monohydrate is effective for (analgesia) and what the chitosan polymer is effective for (to provide substantially linear absorption rates upon administration).

The Examiner also alleges that the term "substantially linear" is indefinite and that the "Applicant has not defined the parameters of substantially, nor provided any means for the examiner to ascertain the meaning." This rejection was addressed in Applicants' March 19, 2008 Response. The Examiner has not responded to the Applicants arguments in the instant Office Action. They are reproduced below for the Examiner's convenience.

While the term "substantially linear" is a relative term, relative terminology is not necessarily indefinite. *See* MPEP §2173.05(b). For example, the Federal Circuit held that one of ordinary skill in the art would know what was meant by the term "substantially equal". *Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819 (Fed. Cir. 1988); See also *In re Mattison*, 509 F.2d 563 (CCPA 1975) (term "to substantially increase the efficiency" deemed definite).

A person of ordinary skill would understand what was encompassed by the term "substantially linear" when read in view of the application as-filed. For example, Figure 1 demonstrates what would be at least substantially linear absorption rate when 15 mg of morphine base was administered with chitosan (triangles), and a substantially non-linear absorption rate when 15 mg of morphine base was administered without chitosan (circles). Similarly, the absorption curves shown in Figure 2 for the 7.5 mg, 15 mg and 30 mg nasal formulations are at

least substantially linear whereas the curves for the IV and oral formulations are not. Applicants request that the indefiniteness rejection based on the term "substantially linear" be withdrawn.

The Examiner also states that the term "purified" is unclear. The Examiner states that a specific purity is not defined by the claim. In response applicants note that breadth does not equate to indefiniteness, and a specific purity need not be recited so long as the term "purified" itself is clear. See MPEP 2173.04. The term "purified" would be understood by persons of ordinary skill to refer to morphine base monohydrate that has been obtained from a less-pure form of morphine base monohydrate. As the Examiner suggests, pharmaceutical grade morphine base monohydrate is generally purified morphine base monohydrate. The Examiner has not responded to these arguments and is again, requested to do so should the present rejection be maintained.

VI. Rejections Under 35 U.S.C. § 103

The claims have been rejected as obvious over U.S. Patent Nos. 5,629,011, 5,955,502, 6,433,040 and 6,387,917, each in view of the Merck Index Monograph 06276. Consistent with the Applicants' August 28, 2007 and March 19, 2008 Responses, the following nomenclature will be used throughout this Response:

U.S. Patent No. 5,629,011: "Illum II";

U.S. Patent No. 5,955,502: "Hansen";

U.S. Patent No. 6,433,040: "Dellamary"; and

U.S. Patent No. 6,387,917: "Illum I".

A. The Claims Are Not Obvious Over Illum II in view of the Merck Index Monograph

Claims 1-2, 4-8, 16-17 and 21-23 stand rejected as obvious over U.S. Patent No. 5,629,011 issued to Illum (hereafter "Illum II") in view of the Merck Index Monograph. Illum II is said to disclose a composition for nasal administration of polar metabolites of morphine, and an absorption-promoting agent such as chitosan.

(i) Illum II Teaches Away From Using the Base Monohydrate Form of Morphine

Applicants have previously argued that Illum II distinguishes and teaches away from using the morphine *base monohydrate*. Instead, Illum II stresses that *polar metabolites* of morphine should be used *in the place of morphine*. Such metabolites include morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). According to Illum II, polar metabolites of morphine, as well as salts of morphine, are not only distinct, but also *superior* to morphine because:

> Morphine-6-sulphate ***which differs from morphine itself*** by having an ionizable group of Carbon-6 at physiological pH has been shown to be a more potent analgesic than morphine following intracerebroventricular administration in mice.
>
> * * *
>
> Data have indicated that, for example, morphine-6-glucuronide and morphine-6-sulphate could be many times more active than morphine.

(Illum II, col. 2, lines 19-23 and col. 3, lines 3-6)(emphasis added).

The Examiner has not responded to these arguments, and is requested to do so should this rejection be maintained. As noted above, Illum II relates to morphine 6-glucuronide and morphine 6-sulphate, and does *not* disclose the base monohydrate form of morphine, much less the specified ratios called for in independent claims 1 and 21. For this reason, it was noted by the Examiner Kishore during the March 12, 2008 interview that Illum II would be removed as a basis to reject the claims as obvious.

(ii) The Merck Index Does NOT Disclose that Generic Morphine is Necessarily in the Monohydrate Form

In view of Ilum II not disclosing use of the claimed morphine base monohydrate, instead directly teaching away from such use, the Examiner relies upon the Merck Index Monograph 6276. The Examiner alleges:

> The Merck Index discloses generic morphine is in monohydrate form.

(June 23, 2008 Office Action, page 6). A similar assertion was made in the Office Action dated November 15, 2008, in which the Examiner asserted:

> Applicant argues that Illum, Hansen and Dellamary do not disclose morphine base monohydrate. The Examiner disagrees. The references disclose morphine. According to the Merck Index, morphine has a formula of $C_{17}H_{19}NO_3 \cdot H_2O$, which applicants claim on page 4 of the specification to be the formula of morphine base monohydrate. It is therefore, the position of the Examiner that the prior art is teaching morphine base monohydrate.

(November 15, 2008 Office Action, page 13).

Applicant responded to the Examiner's position that the generic term "morphine" refers to the morphine base monohydrate in their March 19, 2008 Response. It was noted that "morphine," as reported in the Merck Index (Twelfth Edition) has the formula $C_{17}H_{19}NO_3$. The molecular weight of morphine is listed as 285.34. The Merck index also lists, as a separate entry, the monohydrate form of morphine. The monohydrate form has distinct physical properties as compared to morphine. The formula of the *monohydrate* form of morphine is listed as $C_{17}H_{19}NO_3 \cdot H_2O$, (note the added water), which would correspond to a molecular weight of 303.36.

It was also noted that in addition to the monohydrate form of morphine, the Merck Index (Twelfth Edition) also lists the acetate trihydrate, mucate, tartrate trihydrate and 6-methyl ether forms of morphine (heterocodeine). Each of these, like the base monohydrate, is distinct from morphine itself. If one were to assume that the word "morphine" teaches the base monohydrate form of morphine because of the Merck index's grouping, one would also have to assume that the acetate trihydrate, mucate, tartrate trihydrate and 6-methyl ether forms of morphine are all equivalent. This cannot be the case because the Merck Index discloses that heterocodeine is six times more potent than morphine. Applicants respectfully submit that the assertion that the term morphine is synonymous with morphine base monohydrate is incorrect.

In sum, the secondary reference, the Merck Index, does not remedy the shortcomings of Illum II. While the base monohydrate is listed along with all other forms of morphine and morphine derivatives, there is no teaching or suggestion to select the base

monohydrate form, much less to use the amounts specified in claims 1 and 21. This is particularly relevant given that Illum II teaches that morphine metabolites are superior to other forms of morphine. The Merck Index Monograph thus does not negate the surprising discovery that the specified amounts of chitosan polymer and morphine base monohydrate provide substantially linear absorption upon administration.

In view of the above, Applicants request that the Examiner adhere to Supervisory Examiner Kishore's decision to remove Illum II as a basis for an obviousness rejection, and that the rejection on these grounds be withdrawn.

B. The Claims are Not Obvious Over Illum I In View of the Merck Index Monograph 06276

Claims 1-2, 4-17 and 21-23 stand rejected as obvious over U.S. Patent No. 6,387,917 (hereafter "Illum I") in view of the Merck Index Monograph. Illum I is said to disclose compositions containing a methane sulphonate salt of morphine and chitosan. Illum I teaches converting the base monohydrate form of morphine to the methane sulphonate salt, or alternatively, using the hydrochloric acid form of the drug. Like Illum II, Illum I does not teach the use of unconverted morphine base monohydrate as claimed by the Applicants, nor does the reference teach that the base monohydrate form of morphine could be combined with chitosan at specified molecular ratios to provide an analgesic morphine formulation that provides substantially linear absorption upon administration.

(i) A De Minimus Amount of Morphine Base Monohydrate That May Be Present in Illum I Does Not Render The Claims Obvious

In response to these arguments that the Illum references do not teach use of the base monohydrate form of morphine, the Examiner asserts:

> Applicant argues the morphine base monohydrate in Example 2 of Illum [I] is converted to the methane sulphonate salt of morphine upon the addition of 2M methane sulphonic acid. This occurs prior to the addition of the chitosan solution. The Examiner notes that applicant has employed the terminology comprising allowing for

> the inclusion/addition of any number of components regardless of their material effect on the other components.
>
> While the reference teaches the equimolar amounts of acid to the morphine base, a conjugate base would be present and equilibrium. Therefore, barring a showing to the contrary, it is the examiners position that some morphine base monohydrate would still be present in the final product.

(June 23, 2008 Office Action, page 9).

Applicant respectfully disagrees with the Examiner's assertion that some *de minimus* amount of morphine base monohydrate that *may possibly* be present in Illum I renders the present claims obvious. Applicants note that the claims have been rejected as obvious, as opposed to anticipated, and thus the cited reference needs to be considered in its entirety, including parts that teach away from the present claims. In this regard, it must be acknowledged that the sole purpose of the morphine base monohydrate in Example 2 of Illum I is to prepare the methane sulphonate salt of morphine. Any *de minimus* amount of morphine base monohydrate remaining in the formulation of Illum I is both unintended and undesired. This is because the purpose of Illum I is to "explore the use of alternative salts of opioid analgesics, such as morphine," the methane sulphonate salt in particular having been found to be "advantageous." (See Illum I, col. 2, ll. 30-42.)

It is also noted that pending independent claims 1 and 21 specify a minimum 1:1 ratio of morphine base monohydrate to chitosan polymer which, surprisingly, provides substantially linear absorption of the morphine base monohydrate. Any de minimus amount of the morphine base monohydrate which – contrary to the intent of Illum I – may be present in the formulation of Example 2, will not reach the 1:1 ratio called for in claims 1 and 21. Nor does Illum I disclose or suggest that this increased amount of morphine base monohydrate provides substantially linear absorption upon administration.

(ii) Disclosure of Various Forms of Morphine in the Merck Index Does Not Provide the Missing Teaching

Because Illum I does not disclose the recited molecular ratios of morphine base monohydrate to chitosan, nor that any chitosan-containing morphine formulation can provide substantially linear absorption upon administration, the Examiner has found cause to rely on a secondary reference -- the Merck Index Monograph 6276. The Examiner states (incorrectly) that the Merck Index Monograph teaches that generic morphine is in monohydrate form. This statement misses the point: Why would a disclosure of morphine base monohydrate, with nothing more, render obvious the discovery that this form of morphine, when combined with chitosan at specified molecular ratios, provides linear absorption upon administration? Like Illum I, this missing teaching is not found in the Merck Index.

The Merck Index merely teaches that which applicants do not dispute: namely, that the base monohydrate is a known form of morphine. As both Illum I and Illum II teach, this base monohydrate is not equivalent to other forms of morphine, such as metabolites of morphine or the methane sulphonate salt of morphine. The mere disclosure of the base monohydrate form of morphine, alone, does not render obvious the applicant's discovery that this form of morphine, when combined at specified molecular ratios with chitosan, yields substantially linear absorption upon administration. Because neither Illum I nor the Merck Index disclose or suggest this surprising discovery, and because the Illum references *teach away* from the base monohydrate form of morphine, Applicants request that the obviousness rejection be withdrawn

C. The Claims Are Not Obvious Over Hansen In View of the Merck Index Monograph 06276

Claims 1-2, 4-12, 16-17 20-21 and 23 stand rejected as obvious over U.S. Patent No. 5,955,502 issued to Hansen (hereafter "Hansen") in view of the Merck Index Monograph for morphine. The Examiner states that Hansen discloses the use of a fatty acid ester as bioadhesive substances and that the compositions may further include chitosan, morphine, antioxidants and antimicrobials.

(i) The Examiner Has Not Responded to the Deficiencies of Hansen

As noted in Applicants' March 19, 2008 Response, chitosan is not a fatty acid ester; it is a polysaccharide. Chitosan is mentioned in Hansen as an example of a possible component of an inert core for *oral* administration (see Hansen, col. 12, lines 55-64). Morphine (not morphine base monohydrate) is listed amongst a laundry list of active agents than spans almost an entire column of Hansen. In short, there is absolutely no reason that Hansen would render obvious the discovery that forms a basis for the present application: that combining morphine base monohydrate with chitosan in specific ratios provides substantially linear transmucosal uptake of morphine upon administration.

The Examiner has not explained why the Hansen reference, which *only discloses use of chitosan in connection with oral formulations,* renders the present claims obvious. In particular Hansen teaches:

> The multiple unit composition may be presented in the form of a powder or in the form of a tablet or capsule, optionally provided with a coating such as a film coating, or an enteric coating.
>
> The core of the individual units of the multiple unit compositions may comprise an inert core such as a biodegradable core comprising a polysaccharide selected from the group consisting of carmelose, chitosan, pectins, xanthane gums, carrageenans, locust bean gum, acacia gum, gelatins, alginates, and dextrans, and salts thereof.

(Hansen, col. 12, ll. 55-64).

`In view of the above, the subject matter of Claims 1-2, 4-12, 16-17 and 20-21, and 23, would not have been shown or suggested by Hansen, and as such, Applicants request that this rejection be withdrawn.

(ii) The Merck Index Monograph Does Not Address The Deficiencies of Hansen

Without addressing, *inter alia*, that the chitosan disclosed in Hansen is to be used in oral compositions and that morphine is generically listed amongst a long list of other active agents, the Examiner cites the Merck Index Monograph and notes:

> Hansen does not disclose the morphine is morphine base monohydrate.
>
> The Merck index discloses generic morphine is in monohydrate form.

(June 23, 2008 Office Action, page 11). As noted above, the Merck Index merely confirms that the base monohydrate is one form of morphine. There are numerous other forms of morphine (such as the distinct forms disclosed in Illum I and Illum II). Neither Hansen nor the Merck Index discloses or suggests that *transmucosally delivered* controlled release compositions that include the base monohydrate form of morphine and a chitosan polymer in the ratios specified in claims 1 and 21 provide substantially linear absorption of morphine.

(iii) Not Receiving a Copy of the Merck Index Does not Justify Not Responding to Applicants Remarks

In the "Response to Arguments Section", the Examiner asserts:

> Applicants' arguments have been carefully considered but they are not persuasive. Applicant stated that an Exhibit was attached to the response; however, the Examiner was unable to locate any exhibit submitted.

(June 23, 2008 Office Action, page 15).[1] Even a cursory review of Applicants' March 19, 2008 Response would have informed the Examiner that the attachment was a copy of the Merck Index entry for morphine, a reference that was referenced by the Examiner in the November 15, 2007 Office Action and cited by the Examiner in the present Office Action. It is unclear why not receiving a copy of this reference would prevent the Examiner from commenting upon the

[1] It is noted that the Examiner's Response to Arguments was located after the Dellamary Rejection, discussed below. It is assumed that this Response applies to both the Hansen and Dellamary rejections.

previous statements with respect to Hansen. Nevertheless, a copy of this Exhibit is submitted herewith. Again, the Examiner is requested to specifically respond to the remarks made by the Applicant.

D. The Claims Are Not Obvious Over Dellamary In View of the Merck Index Monograph 06276

Claims 1-2, 4-17 and 20-21 stand rejected as obvious over U.S. Patent No. 6,433,040 issued to Dellamary (hereafter "Dellamary"). The Examiner states that Dellamary discloses methods, systems and compositions comprising relatively stable dispersions of perforated microstructures in a suspension medium.

(i) The Examiner Has Not Responded to the Deficiencies of Dellamary

As noted in Applicants' March 19, 2008 Response, the stable dispersions of perforated microstructures disclosed in Dellamary are preferably administered via a liquid dose for topical administration to the lung and for systemic delivery via the lung. More particularly as noted in the abstract of Dellamary:

> In particularly preferred embodiments the stabilized dispersions may be directly administered to the lung of a patient using an endotracheal tube or bronchoscope.

(Dellamary, Abstract ll. 9-12).

Like Hansen, Dellamary lists morphine amongst a laundry list of active agents. Inclusion of chitosan is merely contemplated, but is not a focus of the compositions of Dellamary. Instead, Dellamary relies upon microstructures suspended in liquid fluorochemical. As Dellamary is directed to an entirely different formulation system it would not have lead one of ordinary skill in the art to the discovery that combining morphine base monohydrate with chitosan in specific ratios provides substantially linear uptake of morphine upon transmucosal administration.

(ii) The Merck Index Monograph Does Not Address The Deficiencies of Dellamary

Without addressing, *inter alia*, that the chitosan disclosed in Hansen is to be used in oral compositions and that morphine is generically listed amongst a long list of other active agents, the Examiner cites the Merck Index Monograph and notes:

> Dellamary does not disclose the morphine is morphine base monohydrate.
>
> The Merck index discloses generic morphine is in monohydrate form.

(June 23, 2008 Office Action, page 13). Again, the Merck Index merely confirms that the base monohydrate is one form of morphine. The Merck Index does not provide further insight as to why a person of ordinary skill in the art would find that a *transmucosally delivered* morphine base monohydrate composition that includes a chitosan polymer in the ratios specified in claims 1 and 21 would provide substantially linear absorption of morphine.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be passed to allowance. If there are any other issues remaining which the Examiner believes could be resolved either through a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. Applicants believe no fee is due at this time. However, if any fees are

required, the Commissioner is authorized to charge such fee to Deposit Account No. 02-4377.

Dated: November 24, 2008

Respectfully submitted,

By _____
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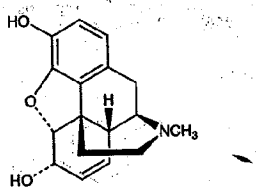
EXHIBIT A

Oily liq, $bp_{0.05}$ 115°.
Hydrochloride, crystals from acetone + ether, dec 229°.
Sulfate, crystals from alcohol + ether, dec 195°.
N-Methylmorphinan, crystals, mp 61°.

6359. Morphine. *(5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol;* morphium; morphia; Dolcontin; Duromorph; Morphina; Nepenthe. $C_{17}H_{19}NO_3$; mol wt 285.34. C 71.56%, H 6.71%, N 4.91%, O 16.82%. Principal alkaloid of opium which contains 9-14% anhydr morphine. Occurs naturally as the (—)-form. Also found in normal brain, blood and liver. Extraction procedures: Achor, Geiling, *Anal. Chem.* **26,** 1061 (1954); Leete, *J. Am. Chem. Soc.* **81,** 3950 (1959). Structure: Knorr, *Ber.* **22,** 1113 (1889); Knorr, Hörlein, *Ber.* **40,** 2032, 3341, 4889 (1907); Gulland, Robinson, *J. Chem. Soc.* **123,** 980 (1925). Total synthesis: Gates, Tschudi, *J. Am. Chem. Soc.* **74,** 1109 (1952); **78,** 1380 (1956); Ginsburg *et al., J. Chem. Soc.* **1951,** 936; **1953,** 1524, 2664; **1954,** 3052. Synthesis of (+)-form: I. Iijima *et al., J. Org. Chem.* **43,** 1462 (1978); of (—)-form: E. J. Bijsterveld, H. J. Sinnige, *Rec. Trav. Chim.* **95,** 24 (1976); H. C. Beyerman *et al., ibid.* **97,** 127 (1978). Biogenesis: Leete, *J. Am. Chem. Soc.* **81,** 3948 (1959). Configuration: G. Stork in *The Alkaloids,* **vol. II,** Manske, Holmes, Eds. (Academic Press, New York, 1952) pp 171-189; Bick, *Nature* **169,** 755 (1952); Rapoport, Lavigne, *J. Am. Chem. Soc.* **75,** 5329 (1953); Bose, *Chem. & Ind. (London)* **1954,** 130; Mackay, Hodgkin, *J. Chem. Soc.* **1955,** 3261; Kalvoda *et al., Helv. Chim. Acta* **38,** 1847 (1955). Infrared and polarographic data: Seagers *et al., J. Am. Pharm. Assoc., Sci. Ed.* **41,** 640 (1952). Toxicity data: M. E. Buchwald, G. S. Eadie, *J. Pharm. Exp. Ther.* **71,** 197 (1941). GC-MS determn in biological fluids: R. Wasels, F. Belleville, *J. Chromatog A* **674,** 225 (1994). Review: K. W. Bentley, *The Chemistry of the Morphine Alkaloids* (Oxford, 1954) 433 pp. Comprehensive description: F. J. Muhtadi, *Anal. Profiles Drug Subs.* **17,** 259-366 (1988). Review of pharmacology of endogenous morphine: S. Benyhe, *Life Sci.* **55,** 969-979 (1994).



Short, orthorhombic, columnar prisms from anisole, dec 254°, also a metastable phase, mp 197°. High melting form sublimes at 190-200° (0.2 mm pressure at 2 mm distance).

Monohydrate, $C_{17}H_{19}NO_3.H_2O$, orthorhombic, sphenoidal prisms, needles from methanol. Dec 254-256° with rapid heating. Darkens on exposure to light. Loses water at 130°. d_4^{20} 1.32. $[\alpha]_D^{25}$ −132° (methanol). pKb at 20° = 6.13; pKa 9.85. pH of satd soln, 8.5. uv max in acid: 285 nm; in alkali: 298 nm. One gram dissolves in about 5000 ml water, 1100 ml boiling water, 210 ml alcohol, 98 ml boiling alc, 1220 ml chloroform, 6250 ml ether, 114 ml amyl alc, 10 ml boiling methanol, 525 ml ethyl acetate. Freely sol in solns of fixed alkali and alkaline earth hydroxides, in phenol, cresols; moderately sol in mixtures of chloroform with alcohols; slightly sol in ammonia, benzene.

Acetate trihydrate, $C_{19}H_{23}NO_5.3H_2O$, yellowish-white powder; slight acetic odor. $[\alpha]_D^{15}$ −77° (water). One gram dissolves in 2.25 ml water, 2 ml boiling water, 22 ml alc, 2 ml alc at 60°, 4.5 ml glycerol, 4.75 ml chloroform. Practically insol in ether. *Keep well closed and protected from light.*

Mucate, $C_{23}H_{29}NO_{11}$, ***galactaric acid compd with (5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol (1:1), morphine hyperduric.***

Tartrate trihydrate, $(C_{17}H_{19}NO_3)_2.C_4H_6O_6.3H_2O$, crystalline powder. Sol in 11 parts water; slightly sol in alcohol. Practically insol in chloroform, ether, carbon disulfide.

6-Methyl ether, $C_{18}H_{21}NO_3$, ***heterocodeine.***

Caution: May be habit forming. This is a controlled substance (opiate) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.12 (1995).

THERAP CAT: Analgesic (narcotic).

THERAP CAT (VET): Analgesic (narcotic), preanesthetic, antitussive, antiperistaltic.

6360. Morphine Hydrochloride. Epimor. $C_{17}H_{20}ClNO_3$; mol wt 321.80. C 63.45%, H 6.26%, Cl 11.02%, N 4.35%, O 14.92%. Toxicity data: M. E. Buchwald, G. S. Eadie, *J. Pharm. Exp. Ther.* **71,** 197 (1941).

Trihydrate, white flakes or crystalline powder; bitter taste. Loses its water of crystn at about 100° and usually becomes yellowish. mp about 200° (dec). $[\alpha]_D^{25}$ −113.5° (c = 2.2 in H_2O, anhydr basis). One gram dissolves in 17.5 ml water, 0.5 ml boiling water, 52 ml alc, 6 ml alc at 60°; slowly sol in glycerol. Insol in chloroform, ether. pH about 5. *Protect from light.* LD_{50} in mice (mg/kg): 226-318 i.v. (Buchwald, Eadie).

Caution: May be habit forming. This is a controlled substance (opium derivative) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.12 (1995).

THERAP CAT: Analgesic (narcotic).

THERAP CAT (VET): Analgesic (narcotic), preanesthetic, antitussive, antiperistaltic. Contraindicated in cats; unreliable in horses.

6361. Morphine Sulfate. *(5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol sulfate salt (2:1);* Kapanol; Moscontin; MS Contin; MST Continus; Oblioser; Oramorph; Relipain; Roxanol. $C_{34}H_{40}N_2O_{10}S$; mol wt 668.77. C 61.06%, H 6.03%, N 4.19%, O 23.92%, S 4.79%.

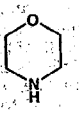
Pentahydrate, ***MST 10 Mundipharma, MST 30 Mundipharma.*** White, fine odorless crystals or powder, or cubical masses. Loses some H_2O at ordinary temp; about $3H_2O$ (7.1%) at 100°, the remainder at 130°. Discolors on exposure to light. mp ~250° with decompn when anhydr. $[\alpha]_D^{25}$ −108.7° (c = 4 in H_2O, anhydr basis). One gram dissolves in 15.5 ml water at 25°, 0.7 ml water at 80°, 565 ml alcohol, 240 ml alcohol at 60°. Insol in chloroform, ether. pH about 4.8. *Keep well closed and protected from light.* Even ampuled aq solns of morphine sulfate will turn brown on storage. No loss of analgesic potency and no increase in toxicity has ever been demonstrated for such discolored solns: *J. Am. Med. Assoc.* **155,** 28 (1954); *J. Pharm. Pharmacol.* **2,** 673 (1950).

Caution: May be habit forming. This is a controlled substance (opium derivative) listed in the U.S. Code of Federal Regulations, Title 21 Parts 329.1 and 1308.12 (1995).

THERAP CAT: Analgesic (narcotic).

THERAP CAT (VET): Analgesic (narcotic), sedative, preanesthetic, gastric sedative. Contraindicated in cats; unreliable in horses.

6362. Morpholine. Tetrahydro-2*H*-1,4-oxazine; tetrahydro-1,4-oxazine; diethylene oximide; diethylene imidoxide. C_4H_9NO; mol wt 87.12. C 55.15%, H 10.41%, N 16.08%, O 18.36%. Prepd by dehydrating diethanolamine: Knorr, *Ann.* **301,** 1 (1898); Jones, Burns, *J. Am. Chem. Soc.* **47,** 2966 (1925); Hampton, Pollard, *ibid.* **58,** 2338 (1936). Toxicity study: H. F. Smyth *et al., Arch. Ind. Hyg. Occup. Med.* **10,** 61 (1954). Review of morpholine and derivatives: A. L. Wilson, *Ind. Eng. Chem.* **27,** 867-871 (1935). *Monograph:* Morpholine Technical Bulletin, Jefferson Chemical Co. (New York, 1953).



Mobile, hygroscopic liquid. Characteristic amine odor. mp −4.9°. bp_{760} 128.9°; bp_6 20.0°. d_4^{20} 1.007. n_D^{20} 1.4540. Volatile with steam. Does not form an azeotrope with water. Flash pt, open cup: 100°F (38°C). Surface tension at 20° = 37.5 dynes/cm. Viscosity at 20° = 2.23 cp. Dipole moment 1.58. Strong base, pKb 5.6. Immiscible with concd NaOH solns. Miscible with water with evolution of some heat, with acetone, benzene, ether, castor oil, methanol, ethanol, ethylene glycol, 2-hexanone, linseed oil, turpentine, pine oil. Will dissolve 109% dimethylamine; 34% trimethylamine; 33% methylamine; >5% naphtha; <1%